UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,512	05/29/2007	Christiane Hollmann	ONCO:006US/10612955	1118

32425 7590 02/01/2010

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
02/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,512	HOLLMANN ET AL.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *5,7 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-4 and 10-16, without traverse, filed November 9, 2009 is acknowledged and has been entered. Claims 5, 7, and 9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 1-5, 7, and 9-16 are pending. Claims 1-4 and 10-16 are under examination.

Specification

2. The disclosure is objected to because of the following informalities: A brief description of the drawings is missing. Applicant is reminded of the proper content of the disclosure.

Content of Specification

(h) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4 and 10-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "A monoclonal antibody … present on fetal red cells including their nucleated precursor cells" because it is unclear what is further "included" with the fetal red cells in addition to their nucleated precursor cells. Does Applicant simply intend, "A monoclonal antibody … present on fetal red cells and their nucleated precursor cells."

Claim 2 is indefinite in reciting, “The antibody according to claim 1, characterized in that it reacts with” because it is unclear what is encompassed by the term “characterized” in relation to the requirements or limitations following the phrase. Perhaps, Applicant intends, “The antibody according to claim 1, having reactivity to…”. See also claim 3.

Regarding claim 2, the phrase "most or all fetal erythroid cells" renders the claim indefinite because it is unclear whether the limitations following the phrase should be part of the claimed invention. See MPEP § 2173.05(d).

Claim 4 is vague and indefinite in reciting, "a monoclonal antibody … present on fetal red cells including their nucleated precursor cells" because it is unclear what is further "included" with the fetal red cells in addition to their nucleated precursor cells. Does Applicant simply intend, "a monoclonal antibody … present on fetal red cells and their nucleated precursor cells."

Claim 10 is indefinite in reciting, "An antibody characterized in that it recognizes or binds specifically to" because it is unclear what is encompassed by the term "characterized" in relation to the requirements or limitations following the phrase. Perhaps, Applicant intends, "An antibody that recognizes or binds specifically to…".

Claim 11 provides for the use of a monoclonal antibody, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 11 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 12 provides for the use of a monoclonal antibody, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 13 is indefinite in reciting, “A method for detection or identification of fetal cells in a sample, characterized by labeling said fetal cells by an antibody according to claim 1” because it is unclear what is encompassed by the term “characterized” in relation to the requirements or limitations following the phrase. Perhaps, Applicant intends, “A method for detection or identification of fetal cells in a sample, comprising labeling said fetal cells by binding them with the antibody of claim 1, wherein the antibody is conjugated with a label.”

Claim 14 is indefinite in reciting, “The method according to claim 13, characterized in that the sample is” because it is unclear what is encompassed by the term “characterized” in relation to the requirements or limitations following the phrase. Perhaps, Applicant intends, “The method according to claim 13, wherein the sample is”.

Regarding claim 15, the phrase "and/or" renders the claim indefinite because it is unclear whether the limitations following the phrase should be part of the claimed invention. See MPEP § 2173.05(d).

Claim 16 lacks clear antecedent basis in reciting, “cells binding the monoclonal antibody” because there is no recitation of “cells binding” in claim 13.

Regarding claim 16, the phrase "or the like" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claim 10 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

In this case, the claimed "antibody" which recognizes or binds specifically to a surface antigen on fetal red blood cells, is a non-statutory subject matter in that it encompasses a naturally occurring product (i.e. autoantibody) of nature which is substantially unaltered, and is not a "manufacture." As an example, "A shrimp with the head and digestive tract removed is an example." Ex parte Grayson, 51 USPQ 413 (Bd. App. 1941).

For statutory subject matter eligibility, patents are not granted for all new and useful inventions and discoveries. The subject matter of the invention or discovery must come within the boundaries set forth by 35 U.S.C. 101, which permits patents to be granted only for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." The subject matter must not be a product of nature, but rather a human-made invention. Herein, the claimed "antibody", encompasses a product of nature present in serum portion of blood but is not made or produced from human ingenuity and research. Accordingly, it is deemed that the claimed antibody recited in claim 10 encompasses non-statutory subject matter.

Perhaps, Applicant intends to recite, "An isolated antibody."

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated 4B9 and 4B8 disclosed in Applicant's disclosure, do not appear to be known and publicly available, or be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the claimed invention or filing of evidence of deposit of all such monoclonal antibodies is required. Without a publicly available deposit of these cell lines other than 4B9 such as those encompassed in claims 1-4 and 11-16, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the disclosed cell line 4B9; the cell lines which produce the chemically and functionally distinct monoclonal antibodies claimed; and/or, the disclosed monoclonal antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same

size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the disclosed monoclonal antibody species, produced by the hybridoma clone accession number DSM ACC 2666.

Deposit Requirements

6. Claims 1-4 and 11-16 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the disclosed biological materials encompassed by the claimed invention are: (1) known and readily available to the public; (2) reproducible from the written description; and/or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

As to Applicant's deposit of the hybridoma clone having the accession number DSM ACC 2666 to the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ, Braunschweig) presumably made under the terms of the Budapest Treaty, an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a

patent, would satisfy the deposit requirement made herein. In order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

This requirement is necessary when a deposit is made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each member State.

7. Claims 1-4 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant discloses monoclonal antibody 4B8 in page 8, lines 18-27 of the specification and Figures 1 and 2 of the Drawings which binds the same epitope as MAb 4B9 which is produced by hybridoma cell having accession number DSM ACC

2666. However, in order for the specification to be complete must include a deposit information for MAb 4B8. Without a publicly available deposit of the above monoclonal antibody, one skilled in the art would not be assured of the ability to practice the claimed invention which encompasses use of disclosed MAb 4B8. Exact replication of the monoclonal antibodies is an unpredictable event. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from the disclosure. If the reproducibility of the monoclonal antibody is established, failure to deposit would result in a concealment of the best mode contemplated by Applicant for carrying out the invention. In re Sherwood, 615.2d 809,204 USPQ 537 (CCPA 1980). Applicants' attention is further directed to In re Lundeck, 773 F.2d 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §§ 1.801-1.809 for information concerning deposit practice.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 4 and 10-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Alvarez et al. (Development, Characterization, and Use of Monoclonal Antibodies Made to Antigens Expressed on the Surface of Fetal Nucleated Red Blood Cells, Clinical Chemistry 45 (9):1614- 1620, (1999)).

Alvarez et al. teach an isolated monoclonal antibody 2B7.4 which binds and reacts with cell surface antigen of fetal red blood cells (RBC), especially their nucleated precursors (nRBCs). Alvarez et al. teach that MAb 2B7.4 recognizes and binds conformationally sensitive epitopes of CD71 (transferin receptor) on the fetal nRBCs; hence, does not bind or react with cell surface antigens on adult erythroid cells (Abstract; p. 1614, col. 2; Table 1; p. 1618, col. 2). The fetal nRBCs are negative for CD45 antigen. MAb 2B7.4 may be conjugated to a fluorophore label (FITC) and used in flow cytometry assays (FACS) to detect and identify the RBCs or NRBCs that are of fetal origin in maternal blood sample and then further conjugated with a magnetic bead to separate or isolate nRBCs using immunomagnetic bead-cell separation (Abstract; p. 1614, col. 2). MAb 2B7.4 is produced by a hybridoma cell (p. 1615, col. 1). The isolated fetal RBCs and nRBCs are used for further analysis of chromosomal or genetic aberration, defects and variants (inherited disease) (p. 1614, col. 2; p. 1618, col. 2).

9. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Bianchi et al. (Erythroid-Specific Antibodies Enhance Detection of Fetal Nucleated Erythrocytes in Maternal Blood, Prenatal Diagnosis, 13: 293-300 (1993)).

Bianchi et al. teach isolated monoclonal antibodies which recognize, bind and react with cell surface antigens present on hematopoietic precursor cells including fetal

RBCs and their nucleated precursors (nRBCs). The antibodies include anti-CD71, anti-CD36, and anti-glycophorin A (anti-GPA) which react and bind to CD71, CD36, and GPA cell surface antigens which are expressed in fetal RBCs and nRBCs (Abstract; p. 294, 4th full par.). The RBCs and nRBCs are negative for CD45 antigen. The anti-CD36 and anti-GPA antibodies react or bind to fetal erythroid cells but do not bind or react with the CD71 cell surface antigen. Monoclonal antibodies to CD71, CD36, and GPA may be conjugated to a fluorescent label and used in flow cytometry assays to detect and identify RBCs or erythroid cells that are of fetal origin in maternal blood sample (p. 294, 3rd full par). The isolated fetal RBCs are further analyzed by polymerase chain reaction (PCR) for chromosomal or genetic analysis of aberration, defects and variants (Abstract, p. 293: Introduction).

10. Claims 1-4 and 10-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuma et al. (US 2003/0180762).

Tuma et al. disclose isolated monoclonal antibodies which recognize, bind and react to intracellular and cell surface antigens present on nucleated precursors (stem) of RBCs or nRBCs of the fetal origin but not to adult (maternal) erythroid cells [0013, 0015, 0052, 0063, 0081]. The antibodies include monoclonal anti-i antibody and monoclonal anti-r antibody which react and bind to intracellular and cell surface antigens expressed in fetal nRBCs [0045, 0046, 0089, 0094]. The RBCs and nRBCs are negative for CD45 antigen which is expressed in white blood cells (WBCs) [0013]. The monoclonal anti-i antibody and monoclonal anti-r antibody react or bind to fetal erythroid cells but do not

bind or react with the CD71 (transferin receptor) cell surface antigen [0036, 0052]. The monoclonal antibodies are produced by a hybridoma cell and may be conjugated to a fluorescent label for use in flow cytometry assays to detect and identify nRBCs or erythroid cells that are of fetal origin in maternal blood sample [0001, 0054-0056, 0063, 0064, 0089]. The isolated fetal RBCs are further analyzed for chromosomal or genetic analysis of mutation, aberration, defects and variants [0001, 0002, 0004, 0081].

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

January 26, 2010